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615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Beat AML S8 Group 2: Gilteritinib (GILT) in Combination with Decitabine (DEC) and Venetoclax (VEN) in Untreated *FLT3* Mutated Acute Myeloid Leukemia (AML) Patients Age ≥60 with High and Low Variant Allele Frequency (VAF)

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Background: GILT is a potent oral selective *FLT3* kinase inhibitor (*FLT3*i) approved for the treatment of patients with relapsed/refractory *FLT3* mutated (*FLT3*m) AML. However, the optimal combination in older, newly diagnosed (ND) *FLT3*m AML patients is unknown. GILT in combination with azacitidine (AZA) had higher initial response rates, but did not improve

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overall survival (OS), compared to placebo in the LACEWING trial (Wang et al. Blood 2021). GILT followed by decitabine (DEC) was also tested and found to be safe, but the efficacy did not meet pre-determined criteria (NCT03013998, S8 Group 1). In the interim, VEN + AZA/DEC emerged as the new standard of care for older/unfit patients with AML (DiNardo et al. NEJM 2020). Thus, the Beat AML S8 study was amended to assess the safety and efficacy of GILT in combination with DEC and VEN in newly diagnosed *FLT3*m AML patients aged ≥60 years (NCT03013998, S8 Group 2).

Methods: The S8 Group 2 sub-study was part of the multicenter (15 sites) Beat AML Master Trial. Key eligibility criteria included ND *FLT3*m AML patients aged ≥60 years who are not able to receive intensive induction chemotherapy, and Eastern Cooperative Oncology Group (ECOG) performance status 0-2. A conventional 3+3 design was used to determine the recommended phase 2 dose (RP2D) of GILT+DEC+VEN. Patients were treated with GILT at three dose levels (DL). During induction, treatment consisted of GILT 120mg/day on days 1-7 then 80mg/day on days 8-28 for dose level 1 (DL1), or on days 8-21 (DL-1), or on days 8-14 (DL-2). All patients received DEC at 20mg/m ^{2} on days 8-12, and VEN at 400mg/day (or at 100mg/day if concomitant antifungal) on days 8-28. Patients who achieved a complete remission (CR) or CR with hematologic improvement (CRh) received GILT 80mg/day on days 1-15 (DL1) or days 1-7 (DL-1, DL-2), DEC on days 1-5 (All DLs), and VEN on days 1-15 (DL1, DL-1) or days 1-10 (DL-2) for an additional 12 consolidation cycles. The primary end point was to determine the tolerability and toxicity of GILT in combination with DEC and VEN. Secondary end point was the composite CR (CRc: CR/CRh) rate. Response was assessed using modified 2017 European LeukemiaNet (ELN) AML criteria.

Results: Between 10/22/2020 and 6/13/2022, 19 patients were consented, of whom 18 started treatment and were included in the analysis. The median age was 73 and baseline patient characteristics are shown in **Table 1**. The first 2 patients treated at DL1 both experienced hematologic dose-limiting toxicities (DLTs) with persistently low absolute neutrophil count (ANC). Therefore, the GILT dose was de-escalated to DL-1, where 8 patients were enrolled and treated. Among the 6 evaluable patients on DL-1, DLTs occurred in 2 patients; one had hematologic DLT and the other had failure to thrive. This led to dose de-escalation to DL-2. In DL-2, 2/8 patients experienced hematologic DLTs. The protocol was then amended to include DL-3 and DL-4, but the trial was closed by the sponsor due to priority transition and enrollment was halted so further dose reductions were not evaluated. Adverse events (AEs) were mostly hematologic, and 11 patients had treatment-related adverse events (TAEs), 10 of them grade 3 or higher. Median (range) time on treatment was 6 (1-25) cycles. Most common reason for treatment discontinuation were adverse event (3, 21.4%), recurrence (2, 14.3%), stem cell transplant (2, 14.3%), and death (2, 14.3%)
Nine patients achieved CR, 2 patients achieved CRh and 1 patient achieved complete remission with incomplete hematologic recovery (CRi). The CRc rate (CR/CRh) was 61.1% (11/18, 95% CI: 38.6%-83.6%). After a median follow up of 19.7 months, the median overall survival and duration of response were not reached. One-year overall survival (OS) was 71.8% (95% CI: 44.9-87.2).

Conclusion: Triplet therapy of GILT+DEC+VEN inND *FLT3*m AML patients ≥60 years old induced a high response rate (CRc rate 61.1%), and the median OS was not reached at time of this report (median follow-up 19.7 months). The typical dose of GILT 120mg/day with DEC+VEN was associated with significant hematology toxicities, which required multiple dose level reductions. At the reduced dose (GILT 80mg/day on days 1-7), the combination therapy was generally safe and well tolerated. A Phase 2 clinical trial sponsored by Astellas of GILT+AZA+VEN as frontline treatment for ND older patients with *FLT3*m AML is now enrolling (NCT05520567).

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Table 1: Patient Demographic and Baseline Characteristics

Characteristic	All Patients (n=18)
Age	
Median (range), years	73 (62, 79)
Age ≥ 75 years, no. (%)	8 (44.4)
Gender, no. (%)	
Female	8 (47.1)
Male	10 (55.6)
Ethnicity, no. (%)	
Caucasian	16 (88.9)
African American	2 (11.1)
ECOG Performance Status, no. (%)	
0	1 (5.6)
1	11 (61.1)
2	6 (33.3)
NPM1, no. (%) Mutated *	7 (36.8)
IDH2, no. (%) Mutated *	2 (11.1)
IDH1, no. (%) Mutated*	1 (5.6)
TP53, no. (%) Mutated*	0 (0.0)
FLT3-ITD, no. (%) Present	13 (72.2)
FLT3-TKD, no. (%) Mutated*	4 (22.2)
VAF=10%	1 (5.6)
TET2, no. (%) Mutated*	6 (33.3)
WT1, no. (%) Mutated*	1 (5.6)

ITD = Internal Tandem Duplication; TKD = Tyrosine Kinase Domain mutation; ECOG = Eastern Cooperative Oncology Group
*VAF of 20% threshold used per Beat AML Master Trial protocol; Genetic testing by LeukoStrat CDx *FLT3* Mutation Assay (InVivoScribe) and FoundationOne Heme (Foundation Medicine).

Figure 1: Overall Survival

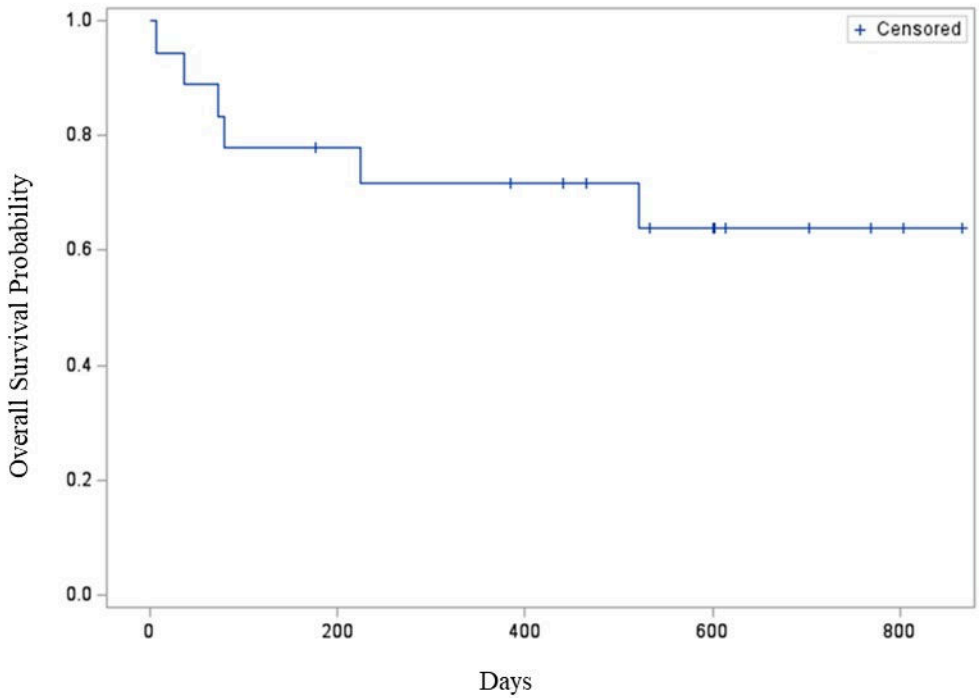

Figure 1